REMARKS

Applicants draw the Examiner's attention to an information disclosure statement with copies of listed documents, filed January 28, 2005. Applicants respectfully request consideration thereof in connection with continued examination of the subject application.

Applicants reiterate the request articulated in the response mailed August 19, 2004 and again ask the Examiner to note the current attorney docket number for the instant application, *i.e.*, 61040-0013-US, and to ensure that the Office records are updated in this respect for future correspondence.

Amendments to Specification

Applicants have amended the specification as filed to insert SEQ ID NO: information into the headers of Appendices 1 and 2, on pages 49 and 138, respectively. Applicants effect this amendment by way of response to the Examiner's comments on the sequence listing, as further discussed hereinbelow. Applicants also draw the Examiner's attention to a preliminary amendment, dated January 28, 2003, in which the specification at page 27 was similarly amended to contain a reference to sequences disclosed in Appendices 1 and 2.

Applicants have also amended the specification to make it consistent with color figures being filed on even date herewith, and as further discussed hereinbelow.

No new matter has introduced by way of the instant amendment, and entry thereof is respectfully requested.

Amendments to the Claims

Claims 44–48, 50, and 39–148 are pending in the instant application. With the instant amendment, Applicants amend claims 137, 142, 144, and 148 to correct various informalities.

Applicants also introduce new claims 149–154 which find support in the specification as filed, as follows: claims 149 and 152, at page 19, lines 23–25; Claims 150 and 153 are supported by a sequence as filed; claims 151 and 154 are supported at page 35, lines 24–25.

No new matter is introduced by the instant amendments and, accordingly, entry thereof is respectfully requested.

The Restriction Requirement

Applicants have considered the office action mailed December 9, 2004 in connection with the above-identified patent application. The Examiner has required restriction of the pending claims under PCT Rules 13.1 and 13.2 to one of the following eight groups:

Group I. Claims 1–25, 72–133, and 140–141, drawn to methods of identifying compounds which modulate nuclear receptor activity or modulate binding of a ligand to a nuclear receptor.

Group II. Claims 29–33, 67–71, and 134–135 drawn to a method of modulating nuclear receptor activity in a mammal.

Group III. Claims 34–35 and 39, drawn to a machine readable storage medium capable of graphical three-dimensional representation.

Group IV. Claims 40–43, drawn to a machine readable storage medium comprising a program for correspondence of data.

Group V. Claims 44–48, 50, 136–138, and 142–148, drawn to a crystal comprising a portion of an estrogen receptor and an agonist.

Group VI. Claims 49 and 51, drawn to a crystal comprising a portion of an estrogen receptor and an antagonist.

Group VII. Claim 139, drawn to a crystal comprising a portion of an estrogen receptor and an agonist.

Group VIII. Claims 52–66, drawn to a computational method of designing a nuclear receptor ligand.

Applicants first thank the Examiner for attending to correcting the placement of claims 25 and 50 as set forth in the list of claim groupings in the office action mailed June 25, 2004.

Applicants also thank the Examiner for re-grouping the claims and for combining claims from groups V and X. Nevertheless, Applicants still disagree with the Examiner's restriction of the remaining groups and, respectfully, request reconsideration thereof. Applicants hereby traverse the restriction as to the remaining groups without disturbing their election of Group V.

Partial Traversal

With respect to the Examiner's division of the instant claims into eight groups and the reasons stated therefor, Applicants respectfully traverse. The Examiner has acknowledged that the "Unity of Invention" standard applies to restriction practice in the instant application (by virtue of the fact that it is a national phase application of International application serial no. PCT/US99/06937). The Examiner has also acknowledged that, under PCT Rule 13.2, unity of invention exists where there is a technical relationship among the claimed inventions that involves one or more "special technical features." Applicant respectfully disagrees with

the Examiner's assessment of the special technical features that are found in the instant claims.

First, the Examiner identifies "the atomic coordinates of helix 12" as being the special technical feature of Groups I, III, and VIII, but not Group II. This analysis overlooks the recitation of "the atomic coordinates of helix 12" in claims 29–33, and in claims 67–71, all of which have been placed in Group II. Thus, at least claims 29–33 and 67–71 currently in Group II could be examined, according to the Examiner's own reasoning, in one of groups I, III, or VIII.

Second, the Examiner states that: "[a]lthough the inventions of Groups I, III and VIII share the same technical feature, they lack unity of invention because they represent more than one use of the atomic coordinates." Applicants find no such requirement of a common use in PCT Rules 13.1 and 13.2, the rules that establish the basis of unity of invention practice. Accordingly, Applicant respectfully submits that the division, into separate groups, of claims that, by the Examiner's own admission possess a common technical feature, is improper. Specifically, Applicants request that the claims in groups I, III, and VIII, as well as at least claims 29–33 and 67–71 in Group II be rejoined for purposes of subsequent examination, at such time as one or more of those groups of claims is elected for prosecution.

Furthermore, as stated in the Response mailed August 19, 2004, Applicant respectfully submits that claims in certain groups possess the following special technical features:

> an atomic structural model of the estrogen receptor ligand binding domain, comprising atomic coordinates of:
> helix 12 of the ligand binding domain;
> a coactivator binding site, and
> a coactivator bound to the coactivator binding site.

With respect to the claim grouping currently in effect, such claims are those found in **Groups I, II, III, and VIII**, not including claims 134, and 135. Accordingly, Applicants respectfully request joinder of such claims that are found in **Groups I, II, III, and VIII** and that possess the special technical features recited by Applicant, when conducting future prosecution of the subject Application.

Applicants state that the foregoing arguments are not be construed as an admission that the claims of any of groups I, II, III, and VIII are obvious over, or are not patentably distinct from, the claims of any other of such groups. Instead, Applicants request concurrent

examination of such claims because they possess a common technical feature, as required by PCT Rules 13.1 and 13.2.

Applicants also respectfully disagree with the Examiner's separation of claim 139 from those in Group V, and its placement into Group VII. The Examiner differentiates Groups V and VII in the following way:

> "[t]he special technical feature for the invention of Group V is the crystal comprising a protein consisting of the tripeptide Met-Asp-Pro fused to the N-terminus residues 297-554 of the human estrogen a-receptor and the agonist .... *** [T]he special technical feature of the invention of Group VII is the polypeptide of [sic] consisting of reside 305-349 of SEQ ID NO: 27 or SEQ ID NO:28 which is not used to make the crystal of the ternary complex of Group V ....

Applicant respectfully disagrees with the Examiner's characterization of group V and respectfully submits that the Examiner has read into the claims of Group V a feature ("the tripeptide Met-Asp-Pro fused to the N-terminus residues 297-554 of the human estrogen α-receptor") that is nowhere recited therein. Applicants take this opportunity to remind the Examiner that the special technical features common to all of the claims in Groups V and VII are: the estrogen receptor ligand binding domain; an agonist bound to the ligand binding domain; and a molecule bound to the coactivator binding site. Thus, Applicant respectfully requests joinder of Groups V and VII for the instant prosecution.

Applicants state that the foregoing arguments are not be construed as an admission that the claims of either of group V are obvious over, or are not patentably distinct from, the claims of group VII, or vice versa.

In summary, for the reasons discussed hereinabove, Applicants respectfully request that the restriction of the instant claims be reconsidered and applied in accordance with the framework set forth herein. Applicants retain the right to petition from the restriction requirement (or allegation of lack of unity of invention) under 37 C.F.R. § 1.144.

Nevertheless, since the Examiner has made the restriction "Final", Applicants hereby accompany the instant traversal with a petition for review of the restriction requirement under 37 C.F.R. § 1.144.

Objections to the Specification

The Examiner has objected to the specification for two informalities: the abbreviations "OHT" and "GRIP1 NR Box II" are allegedly not defined in the specification at least once.

Applicant disagrees with the Examiner in this regard. Both terms are explained in the specification Thus, OHT is the antagonist "4- hydroxytamoxifen", as referenced in the specification as filed, at page 16, line 12.

The term "GRIP1 NR Box II" is expanded upon at page 16 of the specification, at lines 16–17: it is "a peptide derived from the NR Box II region of the p160 coactivator GRIP1". The "box" is a recognition moiety (see, *e.g.*, specification at page 4, lines 15—26, "[m]embers of the p160 family of coactivators ... recognize agonist-bound NR LBDs through a short signature motif ... known as the NR box.") That the coactivator GRIP1 has three such boxes is referenced at page 32 of the specification as filed, page 32, line 12. The term "Box II" references one of these boxes, as would be commonly understood by one of ordinary skill in the art.

Additionally, the abbreviations "NR" and "GRIP1" stand for "nuclear receptor", and "Glucocorticoid Receptor Interacting Protein 1", as would be known to one of ordinary skill in the art. Evidence for this is provided by the publication, Geistingler and Guy, "An Inhibitor of the Interaction of Thyroid Hormone Receptor β and Glucocorticoid Interacting Protein 1", *J. Am. Chem. Soc.*, 123:1525–1526 (2001), a copy of which is attached hereto, and in which both terms are referenced and explained in the text of the left hand column of page 1525. Applicants also supply a copy of a reagent listing for GRIP1, found on the internet at http://www.bioreagents.com as further evidence of use in the art.

Accordingly, in response to the Examiner's objections, Applicant respectfully points out that both of the terms objected to find support in the specification as filed, and would also be well understood by one of ordinary skill in the art.

Sequence Listing

The Examiner has objected to the specification for allegedly failing to comply with 37 C.F.R. § 1.821(d) in respect of referencing sequences that are "set forth in the 'Sequence Listing'". Applicants thank the Examiner for his attention to detail but respectfully point out that, with the exception of the headers to the Tables in Appendices 1 and 2, the molecules called out by the Examiner in the specification do not correspond to sequences that are set forth in the Sequence Listing. For example, the Examiner references molecules identified as "ERα" and "human estrogen receptor α". The molecules referenced in the specification, but not accompanied by a sequence set forth in the sequence listing, have been identified by name only, and not by "a string of particular bases or amino acids". Applicants respectfully

draw the Examiner's attention to MPEP § 2422.03 which explains that an entry in the Sequence Listing is not required under these circumstances. Accordingly, no amendment to the specification is required other than to the headers to Appendices 1 and 2, that have been discussed hereinabove. Similar comments apply to claims 46, 48, 137, 138, 142, and 143, for which the Examiner raised a similar objection.

Drawings

The Examiner is thanked for drawing Applicants' attention to references to color drawings in the application specification. Applicants file herewith, in compliance with 37 C.F.R. §§ 1.84(a)(2), and 1.17(h), three (3) sets of color drawings (corresponding to FIGs. 1A, 1B, 2A, 2B, 3A–3D, 4A, 4B, 5A, 5B, and 6A–6D), and a petition for acceptance thereof. Applicants also amend the specification as filed to reference the language recited by the Examiner, and to correct a reference to "black-and-white" in the reference to Figure 1 on page 7.

Applicants have not herewith provided a color drawing for FIG. 7. At this time, Applicants amend the specification at pages 9 and 10 to delete references to colors in FIG. 7. However Applicants wish to preserve the right to file a replacement color figure for FIG. 7 at a later date.

Applicants submit that the color drawings, as filed herewith, do not introduce new matter into the specification, and entry thereof is respectfully requested.

REJECTIONS OF THE CLAIMS

Rejections under 35 U.S.C. § 112 (¶ 1)

Alleged lack of written description

The Examiner has rejected claims 44–48, 50, and 136–138 under 35 U.S.C. § 112 (first paragraph) as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection.

In respect of claims 44–48, 50 and 142–147, drawn respectively to a cocrystal, the Examiner has stated that Applicants have provided but "a single representative of these crystals" and have, purportedly, "fail[ed] to describe additional representative species of

these crystals by any identifying structural characteristics or properties other than their composition." Applicants respectfully disagree.

Contrary to the Examiner's characterization of the instant specification, Applicants have provided considerable guidance to one of ordinary skill in the art on the "identifying structural characteristics or properties" of the various components of the crystal complex. In fact the instant specification is replete with detailed structural characterization, both verbal and pictorial, of the estrogen binding site and ligands and coactivators that bind to it. Applicants remind the Examiner that, notwithstanding his own position, guidance for examination in this area can be found in the MPEP, at § 2163 II A 3.(a) ii): "Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." Applicants respectfully submit that the specification as filed demonstrates possession of the necessary common features of the claimed genus, and would be recognized as such by one of ordinary skill in the art at the time of filing.

Specifically, obtaining a cocrystal as claimed, but other than one explicitly disclosed, would require obtaining a portion of an estrogen receptor ligand binding domain sufficient to bind an agonist and a coactivator, as well as a suitable agonist and coactivator molecule that bind thereto. Applicants' specification provides a written description of attributes of each of these species (receptor, ligand, and coactivator) sufficient to establish that Applicants had possession of the invention as a whole at the time of filing. Applicants' specification, rather than being a wholly experimental protocol, is a detailed structural analysis that includes teachings of various computer modeling methods that afford one of ordinary skill in the art with a generalized, but detailed, description of the interactions of the estrogen receptor with a ligand and coactivator.

In respect of the portion of the estrogen receptor ligand binding domain, Applicants have provided both diagrammatic and verbal descriptions of the interaction site, including disposition of helical secondary structure elements, and have identified residues that interact with ligands and coactivators. See, *e.g.*, specification as filed, FIGs. 1–8, and at least at pages 7–10, 12–14, 30–35, 42–45 (Examples 3–5) and 46–47 (Example 7). These attributes encompass specific attributes of the representative species whose crystal structure is found in the specification as filed, and are also consistent with attributes of other species falling within the claims.

One of ordinary skill in the art would recognize that Applicants' specification not only describes, in detail, attributes of the estrogen receptor ligand binding domain but also, by inference, reveals just those features that will be present when forming a cocrystal of the type claimed. Since the application as filed discloses homology alignment of various nuclear receptors, showing how various residues in ligand binding domains align with one another (see, *e.g.*, FIGs. 8A and 8B, and page 1, lines 26–27 "sequence conservation between functional regions, or modules, of the receptors is high"), and since the application has also delineated sequences of estrogen receptor residues that include the ligand binding domain (FIGs. 8A and 8B), one of ordinary skill in the art would appreciate that Applicants knew, at the time of filing, the portions of any estrogen receptor sequence that were necessary to create a complex in which a portion of the estrogen receptor ligand binding domain is bound to a ligand and a coactivator. Furthermore, the term "portion" is not as expansive as the Examiner suggests, and finds definition at, for example, page 12, lines 13–19 of the specification as filed. Thus, the Examiner's belief that Applicants' specification fails to provide structural characteristics that "impart a high predictability of structure for any additional crystal" is not well-founded.

Similarly, Applicant's specification as filed describes more than one estrogen receptor ligand known in the art (*e.g.*, DES, and E_2, see specification at page 11, line 11, as well as seven other agonists listed at page 19, lines 23–25). Applicant's specification further teaches one of ordinary skill in the art to design — through computer modeling — an agonist of the estrogen receptor, based in part upon insights gained from the disclosed crystal structure. (See, *e.g.*, specification as filed at page 18, line 14 to page 19, line 27). Thus, such agonists are identified by having certain structural features that interact with specific residues within the estrogen receptor binding site (as given at, *e.g.*, page 18, lines 15–18). Furthermore, Applicants' specification teaches various chemical modifications to a number of known estrogen receptor ligands that would produce other acceptable ligands. See specification as filed, page 18, line 23 – page 19, line 27. Thus it is not correct to say that Applicants have provided no indication that they understood the requisite features of the claimed invention other than the species explicitly disclosed.

Finally, with respect to the coactivator and its binding site, Applicants have described the structure of the binding site including residues that make it up. (See, *e.g.*, Specification at page 14, lines 15–24, and also page 30, line 15 to page 32, line 27). Applicants have also identified key residues in the coactivator binding site that interact with a coactivator molecule

(see, *e.g.*, Specification as filed, page 25, lines 12–17.) Furthermore, the universe of coactivator molecules is not as vast as the Examiner imagines. The specification as filed states that the preferred binding motif found in coactivator molecules is LXXLL. Coactivator molecules containing such a motif can be made from "protein fragments, fusions, or small peptides" (Specification as filed, page 26, lines 21–23). Applicants' specification further references numerous coactivator molecules known to bind to nuclear receptors including the estrogen receptor, (SRC-1, SRC-2, SRC-3, TIF2, as well as GRIP1, see specification, page 3, line 28 – page 4, line 30), and thus provides one of ordinary skill in the art with a clear teaching both that many representative coactivator molecules were contemplated for use with the claimed invention, and that such coactivators possessed common attributes — the NR box residues.

Additionally, Applicants take this opportunity to point out that, in respect of the overall architecture of the estrogen receptor ligand binding domain, the criticality of the position of helix 12 has been established within the instant specification (see, *e.g.*, page 32, line 28 – page 35, line 14). This information, together with the foregoing, provides a compelling basis for one of ordinary skill in the art to appreciate that, at the time of filing, Applicants had possession of the characteristic attributes of the claimed subject material.

With regards to claims 136–138, and 148, drawn to an "isolated and purified complex", the Examiner bases his arguments on the same principles as when rejecting claims to a cocrystal, with the additional statement that the claims cover the complex "in solution, vapor, amorphous precipitate or crystalline form." In response, Applicants refer the Examiner to the remarks hereinabove that demonstrate Applicants' possession of the salient features of the complex at the time of filing regardless of its phase or form. Such remarks are equally applicable to an isolated and purified complex as to a crystal structure.

Furthermore, Applicants do not disagree that claims 136–138 and 148 read on forms other than crystalline forms, but add that the specification teaches one of ordinary skill in the art, at least, a method of obtaining a crystalline form that involves utilizing forms of the complex both in solution and in vapor phase (specification as filed, page 37, lines 4–10). One of ordinary skill in the art, in possession of a crystalline form of the complex (as with any other form) would have the skill requisite to cause the crystal to undergo a phase transition to, say, a vapor form, and would similarly understand how to dissolve the crystal to create a solution form. Thus Applicants respectfully disagree that the instant specification fails to show that Applicants had possession of the invention as claimed at the time of filing.

Accordingly, Applicants respectfully submit that Applicants' specification provides a clear demonstration to one of ordinary skill in the art that Applicants were in possession of the claimed invention at the time of filing, and respectfully request that the rejection of claims 44–48, 50, 136–138 and 142–148 under 35 U.S.C. § 112 (first paragraph) be removed.

Alleged lack of enablement

The Examiner has rejected claims 44–48, 50, 136–138, and 142–148 under 35 U.S.C. § 112 (first paragraph) as allegedly being based on a non-enabling disclosure. Applicants respectfully traverse the rejection.

The Examiner has stated, in a similar fashion to his rejection on the basis of alleged lack of possession of the invention, that the claim covers any estrogen receptor ligand binding domain, and any agonist and any coactivator molecule bound thereto and thus is allegedly not enabled across its full scope. Applicants respectfully point out that, as discussed hereinabove, such a universe of compounds is not as vast as the Examiner suggests. In particular, Applicants have shown that certain specific features would be required of an agonist and a coactivator in order to permit formation of a complex with the estrogen receptor ligand binding domain and such features have been set forth in the specification as filed.

Furthermore, the Examiner suggests (December 9, 2004 Office Action at page 6) that enormous experimentation would be required to obtain an estrogen receptor, its ligand binding domain, and agonist and coactivator molecules that bind thereto. Applicants respectfully disagree. Owing to the high homology amongst nuclear receptors and, given that Applicants disclose the portion of the estrogen receptor sequence that encompassess the ligand binding domain, the amount of experimentation involved in obtaining such a domain from another member of the estrogen receptor family is far from "enormous". Similar principles apply to the identification of agonists and coactivators. Applicants' specification references a number of agonists (page 19, lines 23–25). As discussed hereinabove, Applicants' specification describes a number of modifications of such agonists that may lead to further agonists. Finally, Applicants' specification discloses sequence motifs (*e.g.*, NR Box motifs) that give rise to coactivator binding. Thus, obtaining a suitable coactivator does not require the undue experimentation alleged by the Examiner.

Finally, the Examiner states that the conditions of crystallization of a complex of the protein are highly variable and "may require searching for new crystallization conditions with no expectation of success." The Examiner points to the fact that the two crystal structures

disclosed in Applicants' specification were obtained under different conditions as evidence of this view. Applicants respectfully point out that the two crystal structures in question are for different complexes — one is a ternary complex (agonist/coactivator/receptor) falling within the scope of the claims currently under consideration, the other is a binary (antagonist/receptor) complex. Thus, it should not be surprising that different conditions were employed for each.

In general, however, Applicants respectfully submit that, notwithstanding the uncertainty in experimental procedures that underlies the Examiner's rejection, such uncertainties are just what those of ordinary skill in the art are accustomed to. Thus, as suggested by the Examiner, "crystallization methods for proteins are known in the prior ad [sic]" December 9, 2004 Office Action, at page 5. Even though not every such method is guaranteed of success in every instance, one of ordinary skill in the art understands just which methods can be brought to bear in a given instance. Although the level of experimentation required for a successful crystallization may, in some instances, be significant, it is no more than that which one of ordinary skill in the art is normally accustomed.

Furthermore, contrary to the Examiner's suggestion, Applicants' crystallization conditions, as described in the specification as filed, do offer one of ordinary skill in the art a suitable set of conditions from which to begin. As such, these conditions actually reduce the amount of experimentation one of ordinary skill in the art could expect to endure because they give, in the first instance, a starting set of conditions.

The Examiner concludes by stating that "one skilled in the art would require additional guidance such as information regarding the chemical composition of the complex, the exact amino acid sequence of the proteins and polypeptide" and, "[w]ithout such guidance, the experimentation ... is undue". December 9, 2004 Office Action, at page 6. Applicants respectfully disagree: in general, at least the composition (sequence information, etc.) of the various components of the crystal would be readily determinable by one of ordinary skill in the art. Sequence information for proteins and polypeptides is routinely available by a number of techniques available to one or ordinary skill in the art. Similarly, the chemical make-up of an agonist – such as a small organic molecule – is today routinely determinable by a combination of mass spectrometry, NMR, as well as crystallography.

Finally, Applicants also point out that, by virtue of the atomic structural coordinates presented in Appendix 1, one of ordinary skill in the art is now in possession of a set of coordinates for the complex that actually considerably facilitates the step of structure

determination, once another cocrystal has been successfully obtained. This is regardless of the space group of another related crystal; instead it is predicated on the understanding that the 3-dimensional conformation of the complex itself will not change very much from one crystal environment to another. Thus, far from leaving one of ordinary skill in the art to indulge in undue experimentation in this regard, Applicants have facilitated the enablement of additional embodiments of the claimed invention (see, *e.g.*, specification. p. 27, lines 1–5).

Accordingly, Applicants respectfully request withdrawal of the rejection of claims 44–48, 50, 136–138, and 142–148 for alleged lack of enablement under 35 U.S.C. § 112(first paragraph).

Rejections under 35 U.S.C. § 112 (¶ 2)

The Examiner has rejected claims 44–48, 50, 136–138, and 142–148 under 35 U.S.C. § 112 (second paragraph) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respond to the Examiner's itemized points, as follows:

(a) Claims 44 and 136 have been rejected as allegedly indefinite for reciting the phrases "a protein [sic] of an estrogen receptor" and "binding domain". Regarding the first of these terms, since the claims actually recite "a *portion* of an estrogen receptor" Applicants assume that the Examiner has merely mis-read Applicants' claims. Alternatively, if the Examiner was referencing the claim as drafted, Applicants refer the Examiner to page 12 of the specification as filed at lines 14-19 for a description of "portion of".

With regards to "binding domain", Applicants respectfully disagree with his statement that "[t]he word domain does not identify a specific portion of a protein." As stated in the specification as filed (page 1, lines 26—31), "nuclear receptors can be organized into functional modules" including "a C-terminal ligand binding domain (LBD)". Thus the LBD is a portion of the protein that binds a ligand, separate from those portions that play other roles. The specification as filed describes how to identify the region of the estrogen receptor sequence in which the residues that make up the LBD will be found. (See, *e.g.*, page 28, lines 24—27.) Thus, Applicants respectfully submit that the appearance of the term "binding domain" in the instant claims, as it pertains to the estrogen receptor binding domain, does not render the instant claims indefinite.

(b) The Examiner has objected to the term "derivative thereof" in claim 48. This term is referenced in the specification as filed, at page 26, line 24. One of ordinary skill in the art

would understand the term to mean small variations in structure of the NR-box residues, such as by introduction of trivial substituents or isotopic labels on to the amino acid side chains of such residues, so that the recognition capabilities of the NR-box are not significantly altered. Accordingly such a term as used in the instant claims, is not indefinite.

(c) The Examiner has objected to the recitation of "LXXLL" in claims 137 and 142. Applicants have amended these claims herein to reference SEQ ID NO: 1 in connection with the recited sequence and trust that such amendments render the Examiner's rejection moot.

(d) The Examiner has rejected claims 144 and 148 for referencing the abbreviation "DES". With the instant amendment, Applicants have amended claims 144 and 148 to recite "diethylstilbestrol" in place of DES. Support for such an amendment can be found on page 2 of the specification, at line 6.

Finally, the Examiner has rejected claims 138 and 143 for referencing "GRIP1", an abbreviation that is allegedly undefined. As discussed hereinabove, the term "GRIP1" is known to one of ordinary skill in the art to mean "Glucocorticoid Receptor Interacting Protein 1", as evidenced by the two publications attached hereto as an Exhibit. Accordingly, Applicants see no reason to amend claims 138 and 143 at this time to replace or augment the term, GRIP1. If the Examiner disagrees with Applicants' conclusion, he is kindly asked to rearticulate the rejection, and Applicants will give further consideration to it.

Accordingly, Applicants respectfully request that the Examiner remove the rejection of record of claims 44–48, 50, 136–138, and 142–148 under 35 U.S.C. § 112 (second paragraph.

Rejections under 35 U.S.C. § 102(b)

The Examiner has rejected claims 136 and 137 under 35 U.S.C. § 102(b) as allegedly being anticipated by Heery, *et al.*, *Nature*, 387:733–736, (1997), ("Heery", hereinafter). Applicants respectfully traverse the rejection.

Applicants' claims recite "[a]n isolated and purified protein complex comprising" 3 elements. The Examiner considers that Heery discloses such a complex by virtue of an *in vitro* assay. Applicants respectfully point out this is an incorrect reading of Heery. Nowhere does Heery disclose forming an "isolated and purified" complex, as recited in Applicants' claims. A review of the methods used by Heery (page 736, left hand col.) shows that purifications of the species at various steps is not carried out. Furthermore, the complexes are attached to glass beads upon formation (see, *e.g.*, Heery, p. 736, left hand col.) and thus

are not isolated. Accordingly, such an experimental protocol would lead one of ordinary skill in the art to conclude that the complex that forms during the assay is not pure — because is not necessarily free of other species — and is not "isolated" by virtue of its being bound to a bead.

Accordingly, Heery does not anticipate Applicants' claims 136 and 137 and Applicants respectfully request that the rejection of record be removed.

Allowable subject matter

The Examiner is thanked for drawing Applicants' attention to subject matter that may be considered favorably. Applicants point out claims 144 and 148 as amended herein, and new claims 149–154, filed herewith, and request the Examiner's consideration thereof.

CONCLUSION

Applicants respectfully request that the above-made remarks be made of record in the file history of the present application. Applicants have presented a request that **Groups V and X** be joined and have made a provisional election of the same, with a partial traverse with respect to Groups I, II, III, VII, and VIII, as well as to groups V and X. In the event that such a traverse is not deemed persuasive, Applicants provisionally elect **Group V** for prosecution.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 843-4000.

[SIGNATURE BLOCK AND FEE AUTHORIZATION ON NEXT SHEET]

No fee is believed owed in connection with filing of this amendment and response, other than the claim fee and petition fee, as authorized on separate sheets accompanied herewith. However, should the Commissioner determine otherwise, the Commissioner is authorized to charge any underpayment or credit any overpayment to Morgan, Lewis & Bockius LLP Deposit Account No. 50-0310 for the appropriate amount. A copy of this sheet is attached.

Respectfully submitted,

Date: March 9, 2005 By: Richard G. A. Bone

Richard G. A. Bone
Limited Recognition Under 37 C.F.R. § 11.9(b)
(Copy of Certificate attached hereto)

for Thomas D. Kohler, (Reg. No. 32,797)
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Exhibit
Accompanying Response under 37 C.F.R. § 1.111, mailed March 9, 2005

Geistingler and Guy, "An Inhibitor of the Interaction of Thyroid Hormone Receptor β and Glucocorticoid Interacting Protein 1", *J. Am. Chem. Soc.*, 123:1525–1526 (2001).

and

"GRIP1"
http://www.bioreagents.com/index.cfm/fuseaction/products.print/Product/PA1-846 (last accessed at March 7, 2005).